Exploring the Potential Public Health Benefits of a Respiratory Syncytial Virus (RSV) Vaccine Candidate (Ad26.RSV.preF/RSV preF) among Individuals Aged 65 Years and Older in the UK: A Preliminary Mathematical Modelling Approach

EPH63

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Introduction

- Each winter in the UK, RSV causes approximately 175,000 people aged 65 years and older (YOA) to see their GP, 14,000 to be hospitalised and a further 8,000 deaths. There is no prophylactic vaccine or antiviral treatment for RSV available for this elderly population. This study aims to provide preliminary insights on the potential public health impact of the Ad26.RSV.preF/RSV preF protein vaccine candidate in subjects ≥65 YOA in the UK.

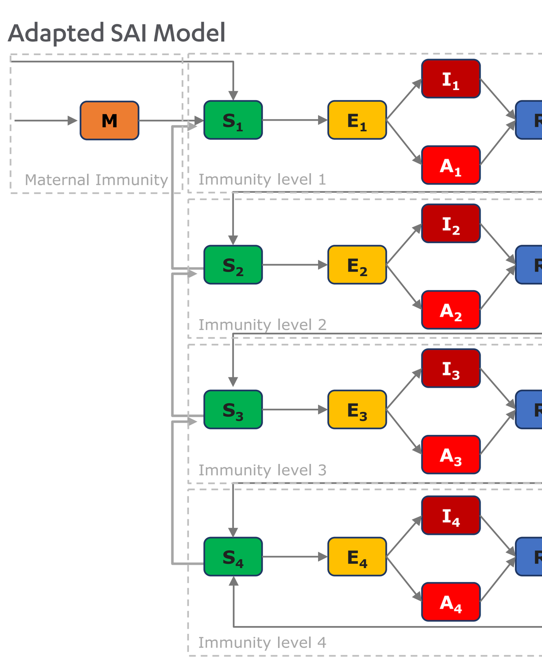
Methods

- A dynamic transmission model (DTM) for RSV was adapted to the UK setting and followed subjects ≥65 YOA over a 20-year time horizon to compare the public health impact of the Ad26.RSV.preF/RSV preF protein vaccine versus no vaccination. Demographic and epidemiological data were derived from UK-specific sources and published literature. The vaccine efficacy was based on clinical trial data and waning rates were assumed in subsequent years. The model was calibrated to digitised data originating from the Respiratory DataMart System (RDMS). Outcomes included RSV symptomatic infections averted, reduction of RSV-related medical attendance, hospitalisations and deaths.

Model structure

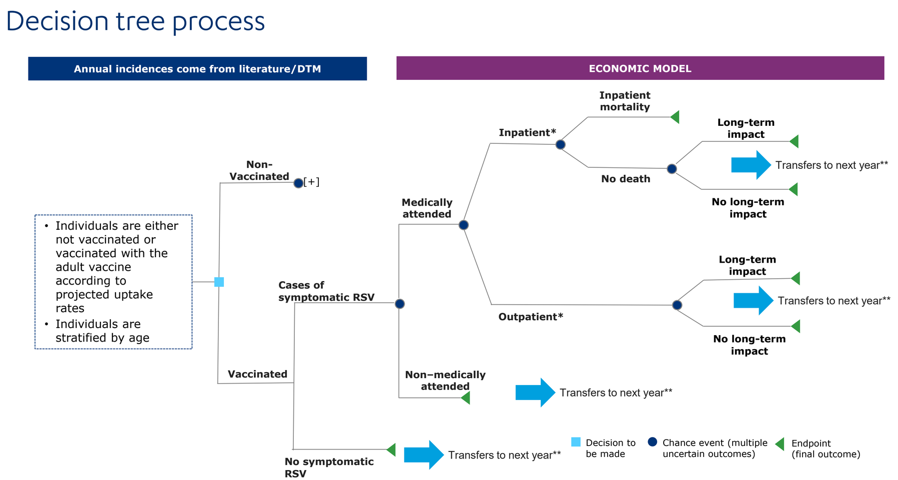
- The model is a DTM for RSV. The model stratifies the population by their epidemiological status (i.e., susceptible, exposed, infectious and recovered), and their vaccination status (unvaccinated and vaccinated).
- A sequential acquisition of immunity ("SAI") approach is used for natural infection. The model has four immunity levels for the first, second, third and fourth (and subsequent) infections and distinguishes between asymptomatic and symptomatic RSV infections.
- Asymptomatic individuals are assumed to be less infectious than symptomatic individuals.
- Vaccinated individuals flow through states over time to account for fixed five-year vaccine protection and all are assumed to be re-vaccinated after five years.

Figure 1. Dynamic transmission model structure



- To assess the public health impact of the vaccine, we developed a hybrid DTM to estimate RSV incidence over time in the UK population and a separate linked decision tree to estimate health outcomes.

Figure 2. Decision tree process



[+] Similar sub-tree

Inputs

- A summary of the key model inputs that are not estimated through calibration are shown in **Table 1**.

Table 1. Model inputs summary

Parameters	Value	Source
Vaccine coverage	73%	Based on UKHSA reports on seasonal influenza vaccine uptake in GP patients (pre-pandemic).
Vaccine efficacy on infectiousness	50%	Sadoff et *al*, 2022
Vaccine efficacy against ARI	66-66-66-60-60%*	Falsey et *al*, 2022 for year 1-3, waning assumed for year 4-5
Mean duration of latency period	5 days	Hodgson et *al*, 2020
Mean duration of infectiousness	5-9 days	
Percentage of asymptomatic RSV infection among all RSV infections (age-group-dependent)	9.1%-52.1%	Munywoki et *al*, 2015
Probability of being medically attended for RSV+ symptomatic ARI (age-group-dependent)	0.3-57.8%	Cromer et *al*, 2017, Taylor et *al*, 2016, Fleming et *al*, 2015
Probability of being medically attended for RSV+ symptomatic ARI (age-group-dependent)	0.3-57.8%	
Probability of hospitalisation for medically attended RSV+ symptomatic ARI (age-group-dependent)	0.6-10.9%	
Mortality for hospitalised RSV+ cases*	0.1%-29.2%	
Cost of RSV hospitalization (per episode)	£3,143.24	NHS reference costs 2020/21 national tariff for healthcare resource group DZ11 Lobar, Atypical or Viral Pneumonia using the mix of non-elective activity data (both short- and long-stay)
Cost per RSV outpatient	£72.10	Assuming surgery consultation and prescription cost from PSSRU

*Outpatient mortality is not included in the base case as a conservative assumption

Calibration

- The DTM was calibrated to demographic and epidemiological data from the UK. Age- and time-specific net migration rates estimated through calibration of underlying demographic model to age-group specific estimated and projected populations sizes over time (ONS database). For the epidemiological calibration a pragmatic, two-step process was adopted to calibrate the model to weekly reported RSV+ samples from July 2010 to June 2017 from RDMS. RDMS contains information on the symptomatic ARI cases who were tested for RSV which will be substantially underreported.

1. Parameters that influenced the model were explored and those that were not deemed influential were fixed.
2. The parameters that were found to be influential were then estimated using a Bayesian, maximum likelihood approach. The likelihood was a negative binomial distribution with mean number of symptomatic infections by age and week.
3. An age-specific detection probability was multiplied to model predicted incident rates to account for the difference between model predicted total RSV cases and those detected in the RDMS surveillance data.
4. Only the fits that gave an incidence rate between 5% to 10% in ≥65 YOA were retained, and only these were used as starting values in incremental mixture importance sampling (IMIS). 41% of the fits satisfied the incidence criterion were used as initial values in the IMIS.

Results

- The resulting parameters from the model calibration process are shown in **Table 2**. The calibrated parameters were tested for correlation, and weak correlation was found between the estimated parameters. The parameters are also in line with other previously published models.

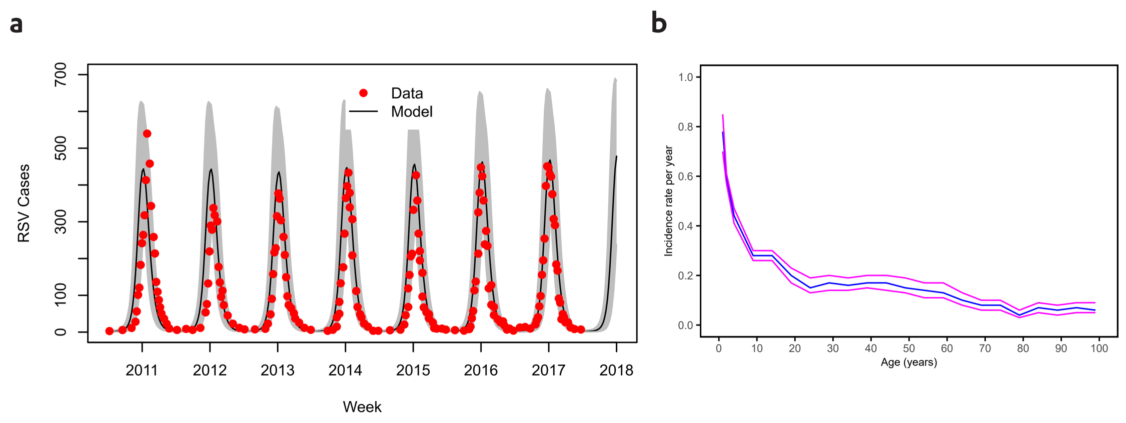
Table 2. Estimated parameters

Parameter	Stratification	Prior distribution	Posterior distribution
Transmission and seasonality			
Per contact transmission probability	None	$U(0.05, 0.25)$	0.180 (0.151 – 0.210)
Amplitude of the seasonal factor	None	$U(0.05, 0.30)$	0.224 (0.153 – 0.289)
Offset (shift) of the seasonal factor	None	$U(0.60, 1.00)$	0.896 (0.840 – 0.952)
Natural history parameters			
Reduction of infectiousness in an asymptomatic infectious state vs a symptomatic infectious state	None	$U(0.50, 0.80)^{\#}$	0.630 (0.530 – 0.730)
Reduction in susceptibility after 2 or more prior infections	None	$U(0.25, 0.50)^{\#}$	0.402 (0.338 – 0.466)
Percentage of asymptomatic RSV infection among all RSV infections in young people and adults (≥15 years)	≥15 years	$U(0.60, 0.85)^{\#}$	0.643 (0.606 – 0.687)
RSV case ascertainment (detection probability)			
The probability that a symptomatic RSV infection is reported in adults	55-64 years	$U(0.00001, 0.01)$	0.265 (0.183 – 0.357) × 10^{-3}
	65-74 years	$U(0.00001, 0.01)$	0.551 (0.347 – 0.781) × 10^{-3}
	≥75 years	$U(0.00001, 0.01)$	1.454 (0.844 – 2.167) × 10^{-3}

$U(a, b)$: uniform distribution between *a* and *b*; CrI: credible interval

#Lower and upper bounds for prior distributions informed by Hodgson's posterior distributions. Parameter sets that produced an incidence between 5% and 10% in adults ≥65 YOA were included in importance sampling.

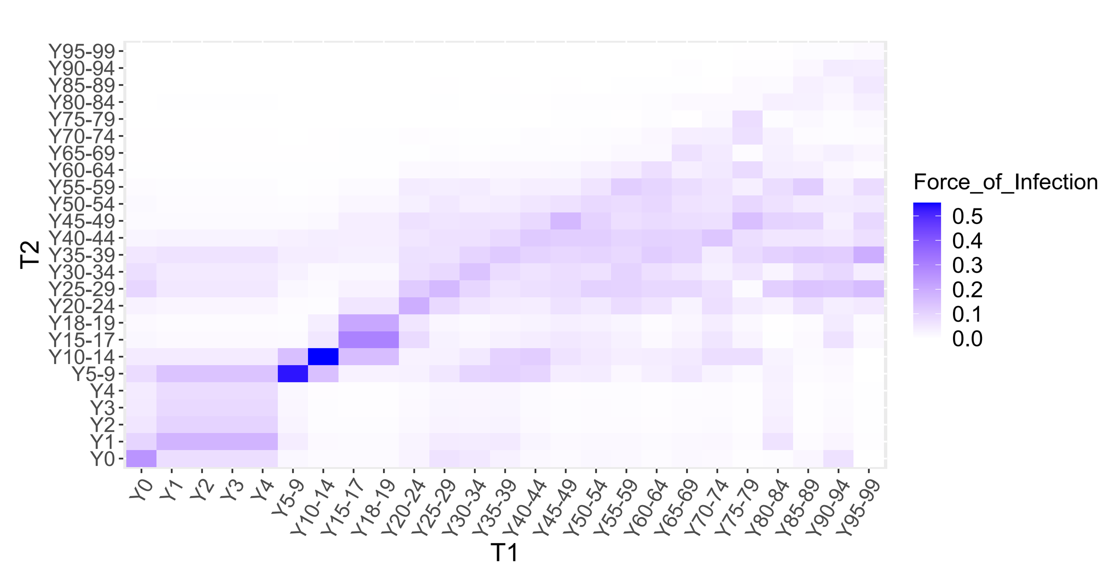
Figure 3. Calibration results and model projections, a) model predicted total RSV incidence over time compared to RDMS data b) projected age specific incidence rates



Note: a) Red: Data points (mean); Grey: lower and upper limits of the 95% credible intervals, b) The mean incidence rate is given by the blue line and magenta lines are the lower and upper 95% bounds of the credible intervals

- The contribution of each age-group to the force of infection is shown in **Figure 4**. This demonstrates that older adults have limited impact on transmission and young children do not seem to contribute to the burden of RSV+ infections seen in the elderly.

Figure 4. Contribution of each age-group to state-state force of infection in the DTM.



Heatmap is illustrative of the contribution each age group has on the force of infection to other age groups. The darker the shade, the greater the contribution.

Burden of disease

- RSV epidemiology projections (all symptomatic RSV+ infections) with and without the impact of vaccination are collated over the time horizon of the simulation (i.e., 20 years).
- The model predicts that the incidence in children <1 year is 78.2% (95% CrI: 70.2%, 85.0%) and an incidence of 6.49% (95% CrI: 5.04%, 8.84%) in those ≥65 YOA (**Figure 3b**). In this elderly population, those over 65–74 years contribute 61.1% (95% CrI: 60.3%, 61.7%) of new cases.
- Despite the huge burden of ARI in children and the elderly, model projections indicate that the burden of RSV in younger adults may be underestimated, although infections in these adults seem to result in less severe outcomes with fewer GP visits, hospitalisations, and deaths compared with the older adults (**Table 3**).
- Model predictions show that the burden of symptomatic RSV+ cases ranges between 10 and 13 million per year in the UK, with the majority of cases occurring in those aged between 5-6 YOA (**Table 3**).

Table 3. Model predictions of the burden of disease in the United Kingdom. Annual RSV+ symptomatic cases between 2010 and 2017

Age group	Number of RSV+ symptomatic cases (per year)	95% Credible Interval
<1 years	503,240	(451,696, 547,360)
1-4 years	1,393,935	(1,324,993, 1,466,740)
5-14 years	2,116,239	(1,950,654, 2,275,609)
15-64 years	6,641,733	(5,649,193, 8,032,501)
65+ years	742,262	(579,153, 1,007,269)
Overall	**11,397,409**	**(10,114,587, 13,264,695)**

Vaccine impact

- The impact of vaccination on symptomatic RSV+ cases are also collated. Results are presented with and without vaccination (ARI and other severe health outcomes) and presented, as well as the numbers needed to vaccinate (NNV) to avoid one such event.
- Over a time horizon of 20 years, the model predicts vaccinating individuals ≥65 YOA in the UK at a 73% coverage rate will result in at least a 48% reduction in symptomatic RSV+ cases, medically-attended RSV+ cases, hospitalised RSV cases, RSV-attributable deaths and total LYs lost, as shown in **Table 4** below, among the vaccinated population and ~1% reduction in the unvaccinated population. As a result, ~£837 million would have been saved from an NHS and Personal Social Services perspective.

Table 4. Model outcomes over 20 years

	No Vaccination (95% CI)	Vaccination (95% CI)	Vaccination Impact (95% CI)
Individuals ≥65 YOA (direct effect)			
Number of vaccine doses administered		-8,696,133 (-12,077,410; -6,666,499)	
Symptomatic RSV+ cases	18,236,950 (14,105,604; 24,996,110)	-3,678,045 (-5,963,388; -2,088,898)	47.68% (47.26%; 48.32%)
Medically attended RSV cases	7,642,831 (4,370,636; 12,274,440)	-292,421 (-525,246; -141,357)	48.12% (47.79%; 48.58%)
Hospitalised RSV cases	601,006 (294,086; 1,068,148)	-75,623 (-145,550; -31,789)	48.66% (48.07%; 49.17%)
RSV-attributable deaths	154,495 (65,034; 297,027)	-477,937 (-921,463; -201,208)	48.95% (48.88%; 49.00%)
Total LYs lost	994,779 (420,870; 1,910,852)	-820,001,493 (-4,707,017,129; -1,942,494,823)	48.04% (47.81%; 48.22%)
Total Cost to NHS (£)	1,711,745,937 (166,146,972; 5,757,056,417)	-8,696,133 (-12,077,410; -6,666,499)	47.90% (47.93%; 47.93%)
Individuals <65 YOA (indirect effect)			
Symptomatic RSV+ cases	216,952,566 (194,124,090; 249,974,752)	-1,746,039 (-1,964,655; -1,598,098)	0.80% (0.82%; 0.79%)
Medically attended RSV cases	18,079,969 (16,401,885; 20,208,113)	-154,820 (-186,386; -142,086)	0.86% (0.87%; 0.92%)
Hospitalised RSV cases	780,975 (732,930; 843,904)	-3,807 (-4,314; -3,302)	0.49% (0.45%; 0.51%)
RSV-attributable deaths	10,116 (8,840; 12,130)	-183 (-238; -156)	1.81% (1.76%; 1.97%)
Total LYs lost	241,111 (214,926; 274,251)	-3,678 (-4,810; -3,287)	1.53% (1.53%; 1.75%)
Total Cost to NHS (£)	2,702,445,888 (368,268,839; 7,515,772,755)	-16,697,183 (-31,125,573; -4,726,423)	0.62% (0.63%; 0.49%)

Table 5. Number needed to vaccinate (≥65 YOA) per averted event

	All averted events (95% CI)	Averted events in Individuals ≥65 YOA (95% CI)
One Symptomatic RSV case	5.2 (4.0; 6.6)	6.3 (4.6; 8.2)
One medically attended RSV case	14.3 (9.3; 24.4)	14.9 (9.2; 26.2)
One hospitalised RSV case	184.8 (103.9; 386.0)	187.2 (104.9; 387.2)
One RSV-attributable death	722.0 (371.5; 1,700.7)	723.8 (372.2; 1,733.8)

Scenario analysis

- Scenarios which explored the impact of varying key model parameters found that increasing vaccine coverage, extending the duration of protection, and producing a greater reduction in infectiousness lead to a greater number of cases and deaths averted, as presented in **Table 6.**

Table 6. Scenario analysis outcomes for individuals ≥65 YOA and <65 YOA over 20 years

	Base Case	Vaccine coverage		Reduction in infectiousness		Duration of protection (with re-vaccination at 5 years)	
		50%	80%	0%	75%	1 year	3 years
Number of vaccine doses administered	54,734,431	37,489,336	59,982,938	54,734,431	54,734,431	54,734,431	54,734,431
Symptomatic RSV cases	-10,442,171	-7,377,899	-11,453,350	-9,029,687	-11,233,728	-2,797,587	-7,389,828
Medically attended RSV cases	-3,832,865	-2,711,939	-4,201,127	-3,575,950	-3,998,044	-998,684	-2,681,475
Hospitalised RSV cases	-296,228	-209,794	-324,457	-280,279	-306,973	-74,337	-203,845
RSV-attributable deaths	-75,806	-53,715	-83,002	-72,078	-78,371	-18,620	-51,679
Total LYs lost	-481,615	-341,026	-526,932	-456,012	-498,294	-125,794	-336,876
Total Cost to NHS (£)	-836,698,675	-591,992,971	-915,906,276	-788,260,732	-867,844,102	-218,454,501	-585,474,924

Summary

RSV burden of disease

- The model projects a significant number of symptomatic RSV cases projected over a 20-year period, suggesting under-appreciation of RSV disease in adults.
- The true public health impact on excess RSV+ deaths among all-cause mortality is underestimated in the base case.
- Younger children do not seem to contribute to the burden in the elderly, underlying the need for a targeted vaccination strategy for the elderly.

Public health impact

- Direct vaccine Impact - Preliminary outcomes suggest a substantial impact of vaccination on the burden of RSV infections in subjects ≥65 YOA in the UK. This reduced burden is primarily driven by direct protective effect of the candidate vaccine.
- Indirect effect impact - Although relative reduction in RSV+ in subjects <65 YOA is small, there is potential for additional public health benefit from the utilisation of the RSV adult vaccine through herd protection, with up to 16.7% of all RSV+ averted through indirect effect.

Conclusions

Preliminary insights suggest a substantial impact of vaccination on the burden of RSV infections in subjects ≥65 YOA in the UK. If confirmed, the programme could be an important public health intervention in alleviating undue pressures on the NHS during RSV seasons. Timely policy for the use of RSV adult vaccines as they become licensed for use and available could be critical to address the high burden of disease and unmet need in the UK population.

Abbreviations: ARI: acute respiratory infections; CEM: cost-effectiveness model; CrI: credible interval; DTM: dynamic transition model; GP: general practitioner; LY: life year; NHS: National Health Services; ONS: Office for National Statistics; RDMS: Respiratory DataMart System; RSV: Respiratory Syncytial Virus; RSV+: RSV-positive; SAI: sequential acquisition of immunity; UK: United Kingdom; YOA: years of age

References **1.** Taylor S, et al. BMJ Open 2016;6: e009337; **2.** Falsey A. Presentation at 12th International RSV Symposium 2022; **3.** Sadoff J, et al. J Infect Dis 2022. 26;226(3):396-406; **4.** Hodgson D., et al. BMC Med 2020; 18(1):348; **5.** Public Health England. Seasonal influenza vaccine uptake in GP patients: winter season 2019 to 2020; **6.** Public Health England. Seasonal influenza vaccine uptake in GP patients: winter season 2018 to 2019. **7.** Public Health England. Seasonal influenza vaccine uptake in GP patients: winter season 2017 to 2018. **8.** Henderson F.W., et al. N Engl J Med 1979; 300(10): 530-4; **9.** Ajufo E., et al. Am J Prev Cardiol 2021; 6:100156; **10.** Munywoki P.K., et al. J Infect Dis 2015; 212(11):1711-8; **11.** Korsten K., et al. Eur Respiratory J 2021; 57(4); **12.** Fleming D.M., et al. BMC Infect Dis 2015; 15(1):1-12; **13.** Cromer, D., et al. Lancet Public Health, 2(8), pp.e367-e374; **14.** ONS. National life tables 2018-2019. 2021.

Author contributions: All authors contributed to the study conception/design, acquisition/analysis/interpretation of data, drafting/critically revising for important intellectual content and the final approval of the publication.

Acknowledgments: This study was funded by Janssen-Cilag Ltd. The authors acknowledge Andreas Nikolaou and Chih-Yuan Cheng for their intellectual contribution to analysis and review of the poster content.

Disclosures: This study is funded by Janssen-Cilag Ltd. T. Shiri, A. Cox, A. Lied-Lied, A. Puggina, L. Hernandez Pastor, and T. Van Effelterre are full-time employees of Janssen-Cilag Ltd. A. Lied-Lied, A. Puggina, L. Hernandez Pastor, and T. Van Effelterre hold stock in Johnson & Johnson. T. Van Effelterre also declares ownership of shares in GlaxoSmithKline. R. Chapman, P. Lozowicki, and C. Duan are employed by Evidera, a consultancy that received funding from Janssen-Cilag Ltd for the work reported here.

Presented at ISPOR EU 2022 Annual Meeting; 6–9 November 2022; Vienna, Austria.